UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/509,302	09/23/2004	Weichang Zhou	21069P	3668

210 7590 05/25/2007

MERCK AND CO., INC
P O BOX 2000
RAHWAY, NJ 07065-0907

EXAMINER	
CHEN, STACY BROWN	
ART UNIT	**PAPER NUMBER**
1648	

MAIL DATE	DELIVERY MODE
05/25/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/509,302	ZHOU ET AL.	
	Examiner	Art Unit	
	Stacy B. Chen	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 March 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-16 and 18-47* is/are pending in the application.

4a) Of the above claim(s) *31-46* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-16,18-30 and 47* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3/30/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment filed March 30, 2007 is acknowledged and entered. Claims 1, 3-16 and 18-47 are pending. Claims 31-46 remain withdrawn from consideration being drawn to non-elected subject matter. Claims 1, 3-16, 18-30 and 47 are under examination.

Response to Amendment

2. The following objections and rejections are withdrawn:

- The objections to claims 4-15 and 19-30 to are withdrawn in view of Applicant's amendment.
- The rejection of claims 1, 16 and 21-24 under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of large scale virus production described in the claims wherein the shear-protective compound is Pluronic® F-68, does not reasonably provide enablement for any other Pluronic® copolymers, hydroxyethyl starch, derivative of cellulose, serum, tryptosephosphate, polyvinyl alcohol (PVA), bovine serum albumin, polyethylene glycol (PEG) or dextran, is withdrawn in view of Applicant's amendment.
- The rejection of claims 1 and 3-15 under 35 U.S.C. 102(b) as being anticipated by Murhammer *et al.* (*Bio/Technology*, December 1998, 6:1411-1418, "Murhammer"), is withdrawn in view of Applicant's amendment. The claims now specify that the cells are mammalian cells, and the teachings of Murhammer pertain to insect cells. Therefore, the rejection is withdrawn.

Claims Summary

3. The claims as amended are drawn to a method of large-scale virus production, specifically, adenovirus production. The method steps are:

a. Inoculate a cell growth medium with a population of mammalian host cells, wherein the medium contains a shear-protective compound, wherein the shear-protective compound is a block copolymer surfactant;

b. Culture the host cells;

c. Infect the host cells with an aliquot of a virus seed stock essentially free of any cell-lysing component;

d. Culture the virus-infected host cells under gas sparging;

e. Harvest intracellular and extracellular virus from the host cells and medium; and,

f. Purify the harvested virus.

Specifically, the shear-protective compound is selected from the group consisting of Pluronic® F-68, other Pluronic® copolymers, hydroxyethyl starch, derivative of cellulose, serum, tryptosephosphate, polyvinyl alcohol (PVA), bovine serum albumin, polyethylene glycol (PEG) and dextran. In embodiments wherein the shear-protective compound is Pluronic® F-68, the concentration is from about 0.3 g/L to about 10 g/L. During the virus production method, gas sparging is provided at a rate up to about 0.1 VVM, or more specifically, a rate up to about 0.001 to 0.05 VVM. Adenoviruses are grown in PER.C6® cells. PER.C6® are known and publicly available at the ECACC, deposit number 96022940.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 3-5, 10-15, 17-20 and 25-30 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention because the claims contain the trademark/trade name Pluronic® F-68. A trademark or trade name is used to identify a source of goods, and not the goods themselves. Thus, a trademark or trade name does not identify or describe the goods associated with the trademark or trade name. In the present case, the trademark/trade name is used to identify/describe polyoxyethylene-polyoxypropylene glycol, and, accordingly, the identification/description is indefinite. The specification teaches that the block copolymer of Pluronic®F-68 is made up of a hydrophobic center (polyoxypropylene block) surrounded by two hydrophilic ends (polyoxyethylene blocks), page 4, lines 30-32.

Applicant's arguments have been carefully considered but fail to persuade. Applicant argues that the specific products of use and their defining characteristics are not only clearly set forth in the specification and claims, but well recognized and appreciated in the scientific literature (Murhammer *et al.*, 1988, *Bio/Technology* 6:1411-1418). In response, the Office has considered the specification and the teachings in the literature regarding Pluronic®F-68. The problem remains that the term itself reveals nothing about the contents of Pluronic®F-68. Although the formula of Pluronic®F-68 may have been constant since its invention, there is no guarantee that "Pluronic®F-68" will remain a copolymer of a hydrophobic center

(polyoxypropylene block) surrounded by two hydrophilic ends (polyoxyethylene blocks). If Applicant is sure that Pluronic®F-68 will only ever be polyoxyethylene-polyoxypropylene glycol, then the term "Pluronic®F-68" may safely be changed to polyoxyethylene-polyoxypropylene glycol without any concern as to changing the scope of the claims. The rejection is maintained for reasons of record. Correction is required.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

(*New Rejection*) Claims 1, 3-16, 18-30 and 47 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jianyong Wu (*Journal of Biotechnology*, 1995, 43:81-94, "Wu"), in view of Brough *et al.* (US Patent 6,113,913, "Brough"), and Murhammer *et al.* (*Bio/Technology*, December 1998, 6:1411-1418, "Murhammer"). The claims are summarized above.

Wu discloses that the industrial application of animal cell cultures for production of biologicals (viral vaccines and other products) requires large-scale cell culture processes, processes that are posed with challenges such as oxygen supply (page 81). Wu teaches that suspension cultures that use sparging aeration can lead to animal cell death (page 81-82, bridging paragraph). Wu discloses that protective medium additives can protect animal cells, such as FBS, Pluronic® F-68, and methylcellulose (page 82, first column, last paragraph). Wu does not

disclose the production of adenoviruses, PER.C6® cells, or the particular concentrations of Pluronic® F-68.

However, Brough discloses that recombinant adenoviruses (E1 deficient) are highly desirable vehicles for gene delivery and transfer (col. 1, lines 9-27) that are produced in PER.C6® cells, which express adenovirus E1 helper function (col. 9, lines 43-45).

Murhammer discloses the scaleup (large-scale production) of insect cell cultures using Pluronic® F-68 as a protective agent against cell lysis (abstract). Murhammer extended the study to include the scaleup of insect cell cultures infected with baculovirus comprising a gene encoding β-galactosidase. The virus seed is expected to be essentially free of any cell-lysing component. Although this particular limitation is not expressly taught, the claim language is broad enough to encompass the presence of some cell-lysing component, if such a component were in the virus seed used by Murhammer. The following method steps are disclosed in the reference:

- Sf9 insect cells were cultured in spinner flasks to provide cells for seeding the spinner flasks and bioreactors (page 1414, last paragraph). TNM-FH medium was supplemented with gentamycin sulfate, Fungizone, heat-inactivated FBS, various concentrations of Pluronic® F-68 (0.2%) and an antifoam compound (see Table 2). Murhammer discloses that although 0.2% Pluronic® F-68 provided full protection from sparging during growth phrase, a higher concentration of Pluronic® F-68 may be required in order to fully protect virally-infected cells (page 1414, first full paragraph).
- Cells were infected with an AcNPV vector containing the *E. coli* β-galactosidase gene (page 1414, last paragraph).
- Infected cells were cultured in a 3-liter water-jacketed bioreactor with a sparger of 7 holes (page 1418, first column, third full paragraph). The sparged reactor was operated at 200 rpm. β-galactosidase synthesis and extracellular virus per 10^6 virally-infected cells in sparged and unsparged systems was measured (Table 2 and page 1418, first column, last paragraph, "Quantitation of virus and β-galactosidase activity").
- The extracellular virus was quantified by collecting the supernatant after centrifuging the cell-virus suspension.
- Murhammer quantified virus titers in PFUs/ml using the $TCID_{50}$ method.

It would have been obvious to perform the scale-up of mammalian cell culture for the production of adenovirus vectors using Pluronic® F-68. One would have been motivated to

propagate adenoviral vectors on a large scale because of their usefulness as gene delivery vehicles (Brough, col. 1, lines 9-27). One would have been motivated to use Pluronic® F-68 in the large scale method because Wu discloses that Pluronic® F-68 is a protective medium additive that can protect animal cells during gas sparging (Wu, page 82, first column, last paragraph). One would have had a reasonable expectation of success that Pluronic® F-68 would have had a protective effect on animal cells infected with adenovirus during gas sparging because Murhammer teaches the propagation of insect cells on a large scale using Pluronic® F-68. On page 1411, top of second column, Murhammer discloses that "Several polymers have been identified which provide protection to mammalian cells in a sparged environment, including the surfactant Pluronic® F-68, which is usually used at a concentration of 0.1% (w/v) or less". Murhammer also discloses that there are "many examples of growing mammalian cells in small-scale, sparged cultures using medium supplemented with Pluronic® F-68", page 1411, second column, first complete paragraph. Given these teachings, one would have known that Pluronic® F-68 is known to protect mammalian cells against gas sparging in small-scale cultures. It is this knowledge that Murhammer uses to derive the scale-up of insect cells with Pluronic® F-68. One would have had a reasonable expectation of success that the scale-up of mammalian cell cultures that use gas sparging would be successful in view of the fact that Pluronic® F-68 is disclosed as protective of mammalian cells. Therefore, the invention as a whole would have been obvious to one of ordinary skill in the art at the time the instant invention was made.

Conclusion

6. No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stacy B. Chen whose telephone number is 571-272-0896. The examiner can normally be reached on M-F (7:00-4:30). If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell can be reached on 571-272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Stacy B. Chen 5/23/07
STACY B. CHEN
PRIMARY EXAMINER